PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference K2365-PCT	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/BE2004/000121	International filing date *(day/month/year)* 25.08.2004	Priority date *(day/month/year)* 26.08.2003
International Patent Classification (IPC) or national classification and IPC A61K9/14		
Applicant K.U. LEUVEN RESEARCH & DEVELOPMENT et al.		

1. This report is the International preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or Industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24.06.2005	19.10.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Veronese, A Telephone No. +49 89 2399-7824

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/BE2004/000121

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-28 as originally filed

Claims, Numbers

1-32 received on 24.06.2005 with letter of 24.06.2005

Drawings, Sheets

1/8-8/8 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/BE2004/000121

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-31
	No:	Claims	32
Inventive step (IS)	Yes:	Claims	20,21
	No:	Claims	1-19,22-31
Industrial applicability (IA)	Yes:	Claims	1-32
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item V.

The following document have been cited in the search report. Where reference is made to them, the following numbering is used; unless otherwise indicated, reference is made to the relevant passages indicated in the Search Report:

D1 : DATABASE WPI Section EI, Week 197930 Derwent Publications Ltd., London, GB; Class S02, AN 1979-G4608B XP002311257 &; SU 627 334 A (FERMENT PRODUCT RES) 21 August 1978.

D2 : US 4 676 439 A (HIRAI AKIRA ET AL) 30 June 1987 (1987-06-30)

D3 : PATENT ABSTRACTS OF JAPAN vol. 2002, no. 04, 4 August 2002 (2002-08-04) &; JP 2001 348581 A (SAWADA SHIGEMI; KOMATSU LTD), 18 December 2001 (2001-12-18)

D4 : DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KUZNETSOV, YU. N. ET AL: "Electromagnetic grinding .of .materials" XP002311255 retrieved from STN Database accession no. 1977:75083.

D5 : DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 1987, SVALOV, S. A. ET AL: "Use of the magneto - induction effect for intensification of grinding" XP002311256 retrieved from STN Database accession no. 1987:481485.

1. Amendments

The applicant has amended claim1 introducing the limitation that the particles are suspended in a liquid, and specifying the linear flow rate through the magnetic field.

2. Novelty (Art.33(2) PCT)

2.1 Claims 1-31

D1 discloses a method for milling powders (of a drug or a food), where the powder is suspended in a magnetic field in the presence of magnetic balls which are transferred in the chaotic state by an alternating magnetic field. A 25% size reduction of the powders is to be expected. **D1** however does not mention that the powder is suspended in a liquid (it seems that the process is carried out in air).
For this reason, the subject matter of claims 1 and 26, and of the respective dependent claims is new over **D1**.

2.2 Claim 32

Despite its wording, claim 32 is a product by process claim directed to a population of biologically active compounds "obtainable" by the process of claims 1 and 27. Since the milling method of the invention does not appear to produce a product characterised by particular technical features, this claim is not novel over any prior art composition comprising particles of an active agent having particle size of 0.45 - 5 micrometers.

3. Inventive step (Art.33(3) PCT)

The problem underlying the present invention is the provision of a process to reduce the dimension of particles (and agglomerates) of biologically active agents.

D3 discloses an apparatus and a process for micronizing liquid micelle particles. The process includes the linear flow of a liquid where the particles are suspended through a strong magnetic field. The applicant's attention is drawn to the figures accompanying the abstract of **D3**.
D3 does not mention the particle flow rate, and the percentage of size reduction. However, it appears that a size reduction of 25% will be obtained with this method, and that the claimed flow rate is what a skilled person would use when using a similar process.
Since claim 1 is not limited to the treatment of solid particles, and also covers liquid particles like the ones disclosed in **D3**, at least a part of the claimed subject matter is obvious. In fact, a skilled person confronted with the underlying technical problem, would use the apparatus and the process disclosed in **D3** as proposed in the present application.
For this reason claim 1, and all dependent claims which are not clearly directed to the treatment of solid particles are not considered to involve an inventive step.
Claims 20 and 21 are considered to involve an inventive step.

D2, D4-D5 disclose a milling process to decrease the particle size of powders, where the particles are suspended in a fluid (air), in a magnet field. The teaching of these documents appears to be limited to a classical milling process where the powder is

suspended in air. Nothing in these documents would prompt a skilled person to carry out the same process in a liquid. For this reason claims 1-31 involve an inventive step over these documents.

4. Industrial Application

The subject matter of claims 1-33 is industrially applicable.

Re Item VI.

WO03072659 and WO2004043580, published after the priority date, but before the filing date, could become relevant in the proceedings before the national authorities of the designated states.
In particular, WO030272659 appears to prejudice the novelty of the claimed subject matter, and also the novelty of claims restricted to the treatment of solid particles.

CLAIMS

1. A method for reducing the average size of biologically active compound particles or agglomerates suspended in a liquid by flowing one or more times said liquid having biologically active compound particles or agglomerates suspended therein through one or more magnetic fields to reduce the average size of a substantial portion of the biologically active compound particles or agglomerates by at least 25%, wherein the linear flow rate of said liquid through each said magnetic field is between 0.25 and 25 m/s.

2. A method according to claim 1, wherein the strength of each said magnetic field is at least about 2,000 gauss.

3. A method according to claim 1 or claim 2, wherein the average size of said biologically active compound agglomerates before performing said method is in a range from about 10 µm to about 100 µm.

4. A method according to any of claims 1 to 3, wherein the average size of a substantial portion of said biologically active compound agglomerates after performing said method is reduced to a range from about 0.45 µm to 5 µm.

5. A method according to any of claims 1 to 4, wherein said substantial portion is at least 50% by weight of the suspended agglomerates.

6. A method according to any of claims 1 to 5, wherein the average particle size of said biologically active compound particles before performing said method is in a range from about 0.5 µm to about 10 µm.

7. A method according to any of claims 1 to 6, wherein the average particle size of said biologically active compound particles after performing is reduced to a range from about 0.5 nm to about 500 nm.

8. A method according to any of claims 1 to 7, wherein the average size of a substantial portion of the biologically active compound particles or agglomerates is reduced by at least 50%.

9. A method according to any of claims 1 to 8, wherein said liquid is water.

10. A method according to any of claims 1 to 8, wherein said liquid is an organic solvent or a combination thereof with water.

11. A method according to any of claims 1 to 10, wherein said biologically active compound particles or agglomerates are suspended in said liquid in the form of a slurry and the concentration of said biologically active compound particles or agglomerates in said liquid is at least two times the solubility limit of said biologically active compound in said liquid under the physical (temperature, pressure) and chemical (pH) conditions prevailing while flowing said slurry through said magnetic field.

12. A method according to any of claims 1 to 11, wherein flowing said liquid through said magnetic field is effected at a temperature between the freezing temperature and the boiling temperature of said fluid under the pressure prevailing while flowing said fluid through said magnetic field.

13. A method according to any of claims 1 to 12, wherein flowing said liquid through said one or more magnetic fields is effected at a temperature between about 2°C and 95°C under atmospheric pressure.

14. A method according to any of claims 1 to 7, wherein the average size of a substantial portion of the biologically active compound particles or agglomerates is reduced by at least 80%.

15. A method according to any of claims 1 to 14, wherein said liquid includes one or more stabilizing agents.

16. A method according to claim 15 wherein the stabilizing agent is a surfactant, a polymer, a silicate, a hydrophilic agent or a combination thereof.

17. A method according to claims 15 or 16, wherein said stabilizing agent comprises a surfactant in an amount such as to produce surfactant-capped nanoparticles.

18. A method according to any of claims 1 to 17, wherein said fluid is re-circulated two or more times through said one or more magnetic fields.

19. A method according to any of claims 1 to 18, wherein the residence time of said liquid through each said magnetic field is between 60 microseconds and 10 seconds.

20. A method according to any of claims 1 to 19, wherein the biologically active compound is in a crystalline form.

21. A method according to any of claims 1 to 19, wherein the biologically active compound is in an amorphous form.

22. A method according to any of claims 1 to 21, wherein the biologically active compound is a drug classifiable as Class II or Class IV of the Biopharmaceutical Classification System.

23. A method according to any of claims 1 to 22, wherein the biologically active compound is a drug having a water-solubility below about 2 mg/ml.

24. A method according to any of claims 1 to 23, wherein the biologically active compound is a drug having a water-solubility below about 5 µg/ml.

25. A method according to any of claims 1 to 24, wherein the biologically active compound is a cosmetic agent, a diagnostic agent, a herbicide, an insecticide, a biocide or a fungicide.

26. A process for manufacturing a biologically active compound formulation, the said process involving the use of biologically active

compound particles or agglomerates, comprising a step of reducing by at least 25% the average size of a substantial portion of said biologically active compound particles or agglomerates, wherein said step includes a method according to any of claims 1 to 25.

27. A process according to claim 26, wherein said process further comprises one or more post-processing steps performed following the size reducing step.

28. A process according to claim 26 or claim 27, wherein said post-processing step is a drying step for substantially removing the liquid in which the biologically active compound particles or agglomerates are suspended during the size reducing step.

29. A process according to claim 28, wherein said drying step comprises freeze drying.

30. A process according to claim 28, wherein said drying step comprises spray drying.

31. A process according to any of the claims 26 to 30, wherein said post-processing step is a step of mixing an adjuvant together with the optionally dried particles or agglomerates with reduced size.

32. A population of biologically active compound particles obtained by a method according to any of claims 1 to 25 or a process according to any of claims 26 to 31.

Box No. VIII (iv) DECLARATION: INVENTORSHIP (only for the purposes of the designation of the United States of America)
The declaration must conform to the following standardized wording provided for in Section 214; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No.VIII (iv). If this Box is not used, this sheet should not be included in the request.

Declaration of inventorship (Rules 4.17(iv) and 51*bis*.1(a)(iv)) for the purposes of the designation of the United States of America:

I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.

This declaration is directed to the international application of which it forms a part (if filing declaration with application).

This declaration is directed to international application No. PCT/ BE2004/000121 (if furnishing declaration pursuant to Rule 26*ter*).

I hereby declare that my residence, mailing address, and citizenship are as stated next to my name.

I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.

Prior Applications: GB 0319797.7

I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name: Guy Van den Mooter

Residence: Pelleberg, Belgium
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Citizenship: BE

Inventor's Signature: .....
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent)

Date: September 13, 2004
(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

Name: Johan Martens

Residence: Huldenberg, Belgium
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Citizenship: BE

Inventor's Signature: .....
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent)

Date: September 10, 2004
(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)

☒ This declaration is continued on the following sheet, "Continuation of Box No. VIII (iv)".

Continuation of Box No. VIII (i) to (v) DECLARATION

If the space is insufficient in any of Boxes Nos. VIII (i) to (v) to furnish all the information, including in the case where more than two inventors are to be named in Box No. VIII (iv), in such case, write "Continuation of Box No. VIII ..." (indicate the item number of the Box) and furnish the information in the same manner as required for the purposes of the Box in which the space was insufficient. If additional space is needed in respect of two or more declarations, a separate continuation box must be used for each such declaration. If this Box is not used, this sheet should not be included in the request.

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Inventor's Signature: .....
(if not contained in the request, or if declaration is corrected or added under Rule 26*ter* after the filing of the international application. The signature must be that of the inventor, not that of the agent)

Date: september 10, 2004
(of signature which is not contained in the request, or of the declaration that is corrected or added under Rule 26*ter* after the filing of the international application)